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Alcohol Use Disorders and Anxiety Disorders: Relation to the P300 Event-Related Potential

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Background: The robust association of alcoholism with reduced P300 event-related potential amplitude has been largely established in severely affected alcoholics and their offspring. Few studies have examined the relationship of increased arousal, anxiety, and P300. In this study, we sought to determine whether P300 group differences could be discerned in well functioning individuals with less severe forms of alcohol use disorders and anxiety disorders. We were particularly interested in looking at the subgroup of alcohol use disorders accompanied by anxiety disorders. This subgroup has previously been found to have diminished α amplitude in the resting EEG.

Methods: Male and female community volunteers (99 unrelated index participants and 78 relatives) and 21 unrelated volunteers from an anxiety disorder clinic were interviewed by using the Schedule for Affective Disorders and Schizophrenia, Lifetime version. Blind-rated lifetime psychiatric diagnoses were assigned according to DSM-III-R criteria. Auditory and visual P300 event-related potentials were elicited with an oddball paradigm and were recorded at the midparietal (Pz) site.

Results: As expected, auditory P300 amplitudes were significantly reduced in participants with alcohol use disorders and significantly increased in participants with lifetime anxiety disorders. However, more detailed analysis revealed that, in an apparent paradox, auditory P300 amplitudes were lowest in individuals with comorbid alcohol use and anxiety disorders and highest in individuals with anxiety disorders alone. Visual P300 amplitudes followed the same trends but were generally not significant.

Conclusions: Even in a sample of largely community-ascertained individuals, auditory P300 amplitude is reduced in alcoholics, particularly those with anxiety disorders, and is highest in nonalcoholics with anxiety disorders.

Key Words: Alcoholism, Anxiety, Auditory, EEG, ERP.

THE P300 EVENT-RELATED potential (ERP) is a scalp-recorded voltage change elicited in response to infrequent, unpredictable, target stimuli occurring among frequent nontarget stimuli. The P300 ERP is a physiologic correlate of attention allocation, basic information processing, and activation and maintenance of working memory (Polich and Herbst, 2000). Variation in P300 amplitude is thought to reflect the degree to which incoming information is processed and incorporated into working memory, as well as the context in which the stimulus occurs (Donchin et al., 1986; Polich and Herbst, 2000). P300 latency is a measure of the speed of stimulus classification (Polich, 1986).

Although P300 amplitudes and latencies are modulated by the nature of the task and the rarity of the anticipated stimulus (the rarer the stimulus, the greater the amplitude), P300 also shows marked interindividual variation. A substantial part of the interindividual variation is attributable to the arousal level of the individual; this is influenced by a variety of factors, including natural biorhythms, fatigue, and the recent consumption of food, alcohol, nicotine, or caffeine (Polich and Kok, 1995). Age is also a factor: P300 latency increases, and amplitude decreases, with age (Goodin et al., 1978; Picton et al., 1984). However, P300 variability may also reflect differences in innate neuroelectrical processing, leading to interindividual variation in cognition and behavior. Indeed, there is convergent evidence that P300 amplitude is heritable: two moderate-sized twin studies found heritabilities of 0.45 to 0.75 for both auditory (O'Connor et al., 1994) and visual P300 amplitudes (Katsanis et al., 1997). A study of 604 individuals from 100 families in the Collaborative Study on the Genetics of Alcoholism (COGA) found heritabilities of 0.32 to 0.36 for auditory, and 0.42 to 0.52 for visual, P300 amplitude (Almasy et al., 1999). Posterior leads tended to be more highly heritable. However, a third study involving 213 twin pairs was unable to distinguish between shared environmental and genetic factors for visual P300 (van Beijsterveldt et al., 1998), perhaps because of the lower cognitive demands of the task used in that study. A quantitative linkage analysis of visual P300 amplitude in a large sample of alcoholics from COGA has identified several potential locations for genes related to P300 generation (Begleiter et al., 1998).

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There is evidence for a genetic influence on P300 latency: COGA found heritabilities of 0.35 to 0.49 for visual, and 0.19 to 0.31 for auditory, P300 latencies (Almasy et al., 1999). One twin study (Katsanis et al., 1997) found substantial heritability (0.63) for a hard visual discrimination task but none for an easy task. However, other studies produced negative (O'Connor et al., 1994) or neutral (van Beijsterveldt et al., 1998) findings.

Individuals with a variety of cognition-impairing behavioral disorders, including alcoholism, schizophrenia, major depression, and anxiety disorders, tend to differ from unaffected individuals in their P300 response. A robust finding is that P300 amplitude is reduced in abstinent alcoholics (Hill and Steinhauer, 1993; Porjesz and Begleiter, 1998). In addition, lower auditory (Cohen et al., 1995) and visual (Patterson et al., 1987) P300 amplitudes have been found in family history–positive alcoholics compared with alcoholics who are family history negative. Both alcoholic and nonalcoholic members of dense alcoholic families in COGA have been shown to have lower P300 amplitudes when compared with controls (Porjesz et al., 1996). Young alcohol-naive sons of fathers with early-onset alcoholism have significantly reduced P300 amplitudes (Begleiter et al., 1984), as do female offspring of male alcoholics from families with a high density of alcoholism (Porjesz et al., 1996). However, not all laboratories have replicated this finding, particularly for auditory paradigms, possibly due to differences in task difficulty (Polich et al., 1994, Whipple et al., 1991) or subject populations (Hill et al., 1999; Holguin et al., 1998). Alcoholism is a heterogenous disease; P300 reduction may in fact be a marker for a subtype (or subtypes) of alcoholism, for example, alcoholism comorbid with antisocial personality disorder (Holguin et al., 1998), conduct disorder (Bauer and Hesselbrock, 1999), or depression (Hill et al., 1999).

Anxiety is a state of increased arousal, behavioral inhibition, and enhanced attention (Gray, 1987); therefore, anxious individuals might be expected to have larger P300 amplitudes. Auditory P300 amplitudes are increased in normal volunteers exposed to anxiety-provoking situations (Grillon and Ameli, 1994). However, they are also increased in anxious, community-ascertained individuals who are not in anxiety-provoking situations (Boudarene and Timsit-Berthier, 1997; Chattopadhyay et al., 1980), and this suggests that increased P300 amplitude might be a trait marker for anxiety.

The P300 response may also be influenced by, or correlated with, underlying personality dimensions, particularly the introversion-extroversion dichotomy. Introverts, being more cortically aroused (Eysenck, 1967), tend to exhibit greater reactivity to sensory stimuli than extroverts (Stelmack, 1990). Some studies (Daruna et al., 1985; Wilson and Languis, 1990), but not others (Cahill and Polich, 1992; Doucet and Stelmack, 2000), have shown that introverts exhibit larger auditory P300 amplitudes than extroverts when tested during monotonous vigilance tasks. This may reflect their greater attentional capacity (DiTraglia and Polich, 1991), or a faster habituation (amplitude decrease over successive trial blocks) may be seen in extroverts (Daruna et al., 1985).

Most ERP studies have been conducted on treatment-seeking patients who have more severe pathology, on offspring of such patients, or on volunteers drawn from atypical groups such as college students or medical staff. The aim of this study was to determine whether auditory and visual P300 group differences could be discerned in community individuals with less severe forms of alcoholism and anxiety disorders, together with a small group of individuals from an outpatient anxiety disorder clinic. As with many previous clinical studies, we focused our study on the midparietal region (Pz), where P300 amplitude is maximal and most heritable and where P300 reduction has been shown to be greatest in alcoholics (Ramachandran et al., 1996). We aimed to look at the relationship between P300 amplitude and lifetime anxiety traits (phobia, panic, and generalized anxiety) in currently nonanxious participants, on whom there are few published studies. We were particularly interested in evaluating a subgroup of alcoholics with anxiety disorders that, in studies on the resting EEG (Enoch et al., 1999), has been shown to have a high frequency of the low-voltage α trait. We hypothesized that in our group of 198 largely community-derived individuals (120 unrelated), P300 amplitude would be reduced in participants with alcohol use disorders, increased in individuals with lifetime anxiety disorders, and negatively correlated with extroversion. We left open the question about P300 amplitude in alcoholics with comorbid anxiety disorders.

METHODS

Recruitment

Index participants (n = 108) were recruited as paid volunteers, independent of phenotype, from the Washington, DC, and Baltimore metropolitan area by newspaper advertisements for a genetic EEG study; the advertisements asked solely for volunteers with a certain family structure (two living biological parents and at least two siblings). A separate group of volunteers (n = 23) was recruited from an outpatient anxiety disorder clinic. In addition to the index participants who responded to the advertisements, 96 family members were recruited because they were closely related to an index participant with low-voltage α, a resting EEG phenotype previously found to be associated with alcohol use disorders and anxiety disorders (Enoch et al., 1999). Of the 227 participants originally recruited, 29 were excluded for reasons described below. Therefore, the final dataset comprised 198 individuals, 120 of whom were unrelated.

Medical and Psychiatric Assessments

Candidates for the study were initially screened by telephone for medical history and for alcohol, drug, and medication use. Exclusion criteria were a history of brain trauma with loss of consciousness, neurological disease (for example, epilepsy or Parkinson's disease), or medications such as anxiolytics or antidepressants.

Two hundred twenty-seven participants passed the initial screening and were studied at the NIH Clinical Center. Informed consent was obtained according to a human research protocol approved by the human research committee of the NIAAA. Participants were medically interviewed by a

Table 1. Participant Demographics and Psychiatric Diagnoses

Variable	Community participants		Anxiety disorder clinic (unrelated; $n = 21$)
	Unrelated ($n = 99$)	Relatives ($n = 78$)	
Mean age (yr)	43.9, SD = 14.4	42.6, SD = 18.8	38.3, SD = 11.5
Sex	F = 56, M = 43	F = 44, M = 34	F = 13, M = 8
Alcohol use disorders	dep = 23, ab = 7	dep = 7, ab = 7	dep = 3, ab = 1
Anxiety disorders	16	12	17
Phobia	9	11	6
GAD	5	1	7
Panic	2	1	5
Two diagnoses	0	1	1
Alc dep + anx dis	5	0	0
Alc ab + anx dis	2	1	1

Alc dep/ab, alcohol dependence, abuse; anx dis, anxiety disorders; GAD, generalized anxiety disorder.

physician and underwent a physical examination and routine blood analyses. Anyone with evidence (as determined by the physician) of neurological disease or an untreated endocrine disorder would have been excluded from further participation at this stage, but none met these exclusion criteria. All participants then underwent a urine test for drugs (drug screen 1, Mayo Clinic), including alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, lysergic acid diethylamide, opiates, phencyclidine, tetrahydrocannabinol, tricyclic antidepressants, and caffeine. Blood alcohol content was estimated from a breath sample.

A psychiatric social worker administered the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L) and the Michigan Alcohol Screening Test (Selzer, 1971). The Eysenck Personality Questionnaire, Revised (EPQ-R; Eysenck and Eysenck, 1975) was administered as a measure of personality traits. The Spielberger State Anxiety Questionnaire (Spielberger et al., 1970) and Beck Depression Inventory (Beck et al., 1988) evaluated state anxiety and depression.

DSM-III-R Diagnoses

Psychiatric (lifetime) diagnoses were made according to DSM-III-R criteria (American Psychiatric Association, 1987) and in blind fashion, as previously described (Enoch et al., 1999). Table 1 documents the prevalence of alcohol dependence, alcohol abuse, and anxiety disorders in both community and clinic-derived participants. The prevalences of anxiety disorders and alcohol dependence in community-derived participants were phobia, 11%; panic, 2%; generalized anxiety disorder, 3%; and alcohol dependence, 17%; these were comparable to US national rates (American Psychiatric Association, 1994).

In this study, "alcohol use disorders" includes DSM-III-R dependence and abuse. The characteristics of the participants with alcohol use disorders have been described elsewhere (Enoch et al., 1999). These 48 participants included 19 women and 29 men. The ratio of DSM-III-R alcohol dependence to abuse was 2:1, both in men and women (Table 1). The participants with alcohol use disorders tended to have early onset of heavy alcohol consumption (22.4 years, SD = 9.0) but were not enriched for antisocial personality disorder ($n = 3$).

As in our earlier studies on this dataset (Enoch et al., 1995, 1999), "anxiety disorders" included phobia, panic, and generalized anxiety disorder. In accordance with DSM-III-R criteria, care was taken to ensure that, if anxiety disorders were temporally or directly related to alcohol consumption, then lifetime diagnoses of anxiety disorders were not assigned.

Characteristics and Demographics of the Dataset

Of the 227 participants originally evaluated, 6 were excluded because ERP records had too much artifact (amplitudes >50 μV in the raw, baseline-corrected EEG), 13 participants had a positive drug screen, and blind-rated SADS-L interviews were unavailable for 8. For the auditory paradigm, a further two participants were excluded because their records had an insufficient number of trials (<20). Of the 29 excluded participants, 11 were index participants (9 community derived, 2 from the anxiety clinic), and 18 were relatives [mostly excluded ($n = 12$) for noncompletion of SADS-L or for a positive drug test]. Therefore, a complete dataset was available for a total of 198 individuals. For the visual paradigm, 5 participants were excluded due to an insufficient number of trials, and hence the complete dataset comprised 195 individuals.

Of the 198 individuals, 113 were women and 85 were men. The mean age was 42.8 years (SD = 16.0). Participants' demographics are given in Table 1.

ERP Acquisition

The P300 ERP is sensitive to many factors, including the acute and withdrawal effects of alcohol, nicotine, and caffeine. Participants were asked to refrain from consuming alcohol and nonprescription drugs for 24 hr before the ERP recording, to sleep well the night before, not to smoke during the procedure, and not to consume more than one cup of coffee on the morning of the test. Nearly all ERP testing was performed in the mornings to minimize possible circadian effects. No participant had a positive breathalyzer test for alcohol or a positive urine test, and none exhibited clinical signs of alcohol withdrawal. Of the 48 participants with alcohol use disorders, 25 had been abstinent for at least 1 year. No participant had a positive urine test for caffeine, implying that none were heavy users, and hence withdrawal effects after a few hours would not be significant. Because smoking was disallowed for only a few hours, it is unlikely that there was a significant nicotine withdrawal effect in the 24% of participants who were smokers. All participants at this stage tested negative for drugs, and because the drug test can detect antidepressants, benzodiazepines, and addictive drugs taken days or weeks before, it is unlikely that participants were experiencing any kind of withdrawal that might affect the ERP.

ERP Data Collection

Data were recorded from gold-plated electrodes applied to 19 scalp sites identified in the International 10-20 System and at two mastoid sites, all with reference to balanced sternovertebral electrodes. Additional electrodes were applied below and lateral to the left eye to monitor electrooculographic (EOG) artifacts. A referential monopolar montage was used to record EOGs because the records obtained are less contaminated by frontal EEG. Electrode impedance was usually less than 3 kΩ but always less than 5 kΩ.

Because participants ranged in age and intellectual ability, the oddball paradigm was designed such that tasks would not be too hard or too easy for anyone. Each participant was seated in a darkened, sound-attenuated room fixating on a black cross at the center of a white screen at a distance of 270 cm. Two independent streams of auditory and visual stimuli (not temporally synchronized) were presented in oddball sequence during each of eight runs to permit the recording of a range of evoked potentials and ERPs in a single paradigm. The results for P300 alone are reported here. Participants were directed to focus on either the visual or the auditory stimuli. The visual stimuli were based on a paradigm described by Begleiter et al. (1984). Seventy-five percent of the trials in random sequence were of a simple oval (nontargets), and the remaining 25% of trials (targets) resembled an outline of a head, as viewed from above, with a nose and one ear. Each image was projected for 25 msec, with an intertrial interval of 2 to 3.5 sec (rectangular distribution). While the visual images were being projected, 750-Hz nontarget and 1500-Hz target tone pips were presented at 0.85 and 0.15 probabilities, respectively, through binaural insert earphones at constant 800-msec interstimulus intervals. The pips were presented for 6.0 msec [with 2-msec rise/fall time in constant phase (cosine-tapered slope)] at 50 dB above each participant's previously tested minimum hearing threshold (typically 80–88 dB) and were mixed with constant low-intensity (30 dB) white noise to mask external sounds. The short duration stimuli, perceived as clicks, were used to enable simultaneous recording of short latency evoked components (not described here).

Participants had no difficulty discerning differences in pitch: the mean hit rate for accurate responses was 96% (SD = 8.0).

During the attend-visual conditions, participants were asked to ignore the auditory stimuli and focus only on the visual images. Participants responded to the target images with a button held in each hand. A plain oval required no response. Heads with an ear on the left or right required left and right button presses, respectively. This task was performed well: the mean hit rate for accurate responses was 81% (SD = 15.0).

During the attend-auditory conditions participants were asked to watch, but not respond to, the visual stimuli, and to press a single button in response to target clicks, making no response to nontarget clicks. Participant compliance was verified via closed-circuit video and by monitoring horizontal and vertical EOGs for any signs of movement.

Each individual participated in an attend-visual and an attend-auditory practice run. This practice session improved accuracy and diminished the possibility of habituation during the actual trials. Data were obtained in eight runs that lasted 220 sec each. Runs 1, 2, 7, and 8 were attend-visual and runs 3, 4, 5, and 6 were attend-auditory. Participants took a 5-min break between runs 4 and 5, during which they completed the Spielberger State Anxiety Inventory and the Beck Depression Inventory. Responses for given stimulus types were averaged over runs of the same type. The attended auditory stimuli totaled 935 nontargets and 153 targets, whereas the attended visual stimuli totaled 240 nontargets and 80 targets (40 left and 40 right).

ERP Analysis

An automated routine was used to eliminate gross artifacts (amplitudes >50 μV in the raw baseline corrected EEG), and the residual EEG was used to construct the number of trials. Although a minimum of 20 trials was considered acceptable, the mean number of trials was 92 (SD = 25), out of a total of 153, for the auditory paradigm and 60 (SD = 15), out of a total of 80, for the visual paradigm.

The recording bandpass was 0.1 to 50 Hz (3-dB roll-off). ERP averages were constructed relative to the mean of a prestimulus baseline of 135 msec and continuing for 695 msec after the stimulus, for visual and auditory targets during attend-visual and attend-auditory, respectively. The ERP thus derived was then submitted to a digital low-pass filter, constructed with a 27-tap (135 msec) symmetrical finite impulse response, by using a Kaiser window with a low-pass frequency of 14 Hz (0.1 dB maximum attenuation ripple), a stopband frequency of 32 Hz (40 dB minimum attenuation ripple), and a 3-dB down-response at 20.2 Hz. The characteristics of this filter were chosen carefully so that sufficient high-frequency noise (e.g., 20+ Hz) could be eliminated without attenuating slower, later response components.

Measures of P300 amplitude and latency were derived from the attended target ERPs for each electrode position. P300 was measured as the positive-most peak (with respect to a 135-msec baseline) within a post-stimulus window of 250 to 675 msec (auditory P300) or 275 to 675 msec (visual P300), separately for each data channel.

Data presented here are based on P300 from the Pz electrode site, where its amplitude was maximal in at least 95% of participants. Measurements were obtained algorithmically and were confirmed by visual inspection.

Statistical Analyses

As expected, P300 amplitude was inversely correlated with age; hence auditory and visual P300 amplitude values were subjected to an age correction by using linear regression. ANOVAs were performed in the unrelated study participants to test our hypothesis that P300 amplitudes would differ among the four clinical groups: alcohol use disorder (alc dep/abuse) participants with and without anxiety disorders and nonalc dep/abuse participants with and without anxiety disorders. Simple regression analyses were used to determine whether state anxiety or state depression scores were correlated with age-adjusted P300 amplitudes and to test for a hypothesized relationship between age-adjusted P300 amplitudes and EPQ-R trait extroversion scores. We repeated the statistical tests in the total group of participants to see whether effect sizes remained stable.

RESULTS

Our study sample consisted largely of community-derived individuals: 99 unrelated individuals and 78 relatives. It could be argued that the additional 21 participants from the outpatient anxiety disorder clinic would have more severe pathology. However, it can be seen from Table 1 that the prevalence of alcohol use disorders was considerably less in clinic individuals than in the sample of unrelated participants from the community, although the proportion of dependence to abuse was the same. The prevalence of anxiety disorders was obviously higher. However, there was no difference in mean auditory P300 amplitude between the 16 anxiety disorder, nonalc dep/abuse clinic participants and the 20 anxiety disorder nonalc dep/abuse community-derived participants [14.0 (SD = 6.2) vs. 12.9 (SD = 4.5) μV, $p = 0.767$, 15 *df,* paired *t* test]. Therefore, we included both sets of individuals in our group of 120 unrelated participants.

Mean P300 Amplitudes and Latencies

The results are derived from the Pz electrode site, where auditory and visual P300 amplitudes were maximal in at least 95% of the participants. The amplitude and latency means were auditory P300 10.8 μV (SD = 5.1) and 364 msec (SD = 47), respectively, and visual P300 16.3 μV (SD = 6.2) and 454 msec (SD = 62), respectively. As expected, auditory and visual P300 amplitudes were strongly correlated ($r = 0.58$, $F = 96.9$, 1 *df,* $p < 0.0001$].

As already discussed, the focus of the hypotheses for this study is P300 amplitude, but nevertheless, ANOVA showed no differences in P300 latencies between alc dep/abuse and nonalc dep/abuse participants ($p \geq 0.824$). Individuals with anxiety disorders had shorter latencies than those without anxiety disorders, but only for auditory P300 ($F = 4.3$, 1 *df,* $p = 0.040$) and not for visual P300 ($F = 0.6$, 1 *df,* $p = 0.427$) latencies.

Assessment of Task Performance

Participants had little difficulty performing the tasks; the average correct response rates were auditory stimuli, 96% (SD = 8), with a mean reaction time of 398 msec (SD = 97); and visual stimuli, 81% (SD = 15), with a mean reaction time of 523 msec (SD = 84). ANOVAs were performed to determine possible behavioral differences among the four groups: alc dep/abuse participants with and without anxiety disorders and nonalc dep/abuse participants with and without anxiety disorders. ANOVA revealed no differences for auditory and visual reaction times, nor for correct response rate to auditory targets. However, there was a difference for correct response to visual stimuli ($F = 3.5$, 3 *df,* $p = 0.016$), because alc dep/abuse partici-

Table 2. Auditory P300 Amplitude and Alcoholism

Variable	Alcohol use disorder			Non–alcohol use disorder					
	n	Mean (μV)	SD	*n*	Mean (μV)	SD	*F* value	*df*	*p*
All unrelated	34	9.9	5.0	86	11.8	5.2	3.2	1	0.074
Female unrelated	14	8.6	5.6	55	12.6	5.1	6.6	1	0.012
Male unrelated	20	10.9	4.4	31	10.4	5.1	0.1	1	0.729
All participants	48	9.2	4.8	150	11.3	5.0	6.4	1	0.013
All females	20	9.1	5.1	95	11.6	4.9	4.6	1	0.034
All males	28	9.4	4.6	55	10.7	5.1	1.3	1	0.254

pants with anxiety disorders were less accurate (73%, SD = 23) than nonanxious alc dep/abuse participants (81%, SD = 17) and anxious (87%, SD = 14) and nonanxious (80%, SD = 13) nonalc dep/abuse participants.

Effects of Age and Sex on P300 Amplitude

In the group of unrelated participants (mean age, 43.0 years; SD, 14.0; range, 17 to 74 years), age was not correlated with auditory P300 amplitude ($r = 0.12$, $F = 1.8$, 1 *df*, $p = 0.185$). In the total group of participants (mean age, 42.8 years; SD, 16.0; range, 15 to 90 years), auditory P300 amplitude decreased with increasing age ($r = 0.23$, $F = 11.1$, 1 *df*, $p = 0.001$), as did visual P300 amplitude ($r = 0.20$, $F = 4.9$, 1 *df*, $p = 0.030$, in unrelated individuals). Auditory and visual P300 amplitudes of all participants were therefore subjected to an age correction with linear regression, and the resulting age-adjusted values were used in subsequent analyses. Auditory and visual P300 amplitudes did not differ between male and female participants.

P300 and Alcoholism

Twenty five of the 48 alc dep/abuse participants had been abstinent from alcohol for at least 1 year. However, ANOVA showed that there was no difference in auditory ($F = 0.1$, 1 *df*, $p = 0.763$) or visual ($F = 0.3$, 1 *df*, $p = 0.573$) P300 amplitude between those who were abstinent and those who were currently drinking. There was also no difference in auditory ($F = 0.2$, $p = 0.620$, 1 *df*) or visual ($F = 0.0$, $p = 0.961$, 1 *df*) P300 amplitude between alcoholics with dependence or abuse.

Table 2 shows the results of ANOVA of the main effect of alcohol use disorders on auditory P300 amplitude. As predicted, P300 amplitude was reduced in alc dep/abuse participants compared with those without those diagnoses. The effect size was approximately the same in female and male alc dep/abuse participants, but female nonalc dep/abuse participants had higher P300 amplitudes.

P300 and Anxiety Disorders

The mean auditory P300 amplitude of the 33 unrelated individuals with anxiety disorders was higher than in the 87 participants without anxiety disorders [12.2 (SD = 6.3) vs. 11.0 (SD = 4.7) μV, $F = 1.3$, 1 *df*, $p = 0.253$], and this difference was significant for the total group [12.1 (SD = 6.0) vs. 10.4 (SD = 4.6) μV, $F = 4.1$, 1 *df*, $p = 0.043$]. Visual P300 amplitudes did not differ significantly between individuals with anxiety disorders and those without.

Table 3. Relationship of Auditory P300 Amplitude to Alcohol Use and Anxiety Disorders: Unrelated Participants

Diagnosis	*n*	P300 amplitude (μV)	
		Mean	SD
Alc+/anx+[a]	8	7.5	6.2
Alc+/anx−[b]	26	10.7	4.4
Alc−/anx+[c]	25	13.7	5.6
Alc−/anx−[d]	61	11.1	4.9

ANOVA: $n = 120$, $F = 3.5$, 3 *df*, $p = 0.018$.

Pairwise comparisons	*F*	*df*	*p*
Alc+/anx+ vs. Alc−/anx−	3.5	1	0.066
Alc+/anx− vs. Alc−/anx−	0.2	1	0.732
Alc−/anx+ vs. Alc−/anx−	4.6	1	0.036

[a] Alcohol use disorders with anxiety disorders.
[b] Alcohol use disorders without anxiety disorders.
[c] Anxiety disorders without alcohol use disorders.
[d] No alcohol use disorders or anxiety disorders.

There was no difference in Spielberger State Anxiety Questionnaire scores between participants with and without anxiety disorders ($F = 1.1$, 1 *df*, $p = 0.290$). Spielberger scores showed no correlation with auditory P300 amplitude ($r = 0.10$, $p = 0.190$). There was no correlation between Beck scores for state depression and auditory or visual P300 amplitudes.

P300 and Alcoholism with Anxiety Disorders

The ratio of dependence to abuse in alcoholics with anxiety disorders (1.3:1) was half that in alcoholics without anxiety disorders (2.5:1; Table 1). There was no difference between alc dep/abuse participants with and without anxiety disorders for (1) abstinence: the proportion of those who were abstinent, (2) age of onset, or (3) years of drinking.

To evaluate the interaction of alcoholism and anxiety disorders in auditory P300 amplitude, an ANOVA was performed in the 120 unrelated individuals, divided into the following four groups: alc dep/abuse participants with and without anxiety disorders and nonalc dep/abuse participants with and without anxiety disorders. There were significant differences between the groups ($F = 3.5$, 3 *df*, $p = 0.018$; Table 3). In pairwise comparisons with nonanxious, nonalc dep/abuse participants (Table 3), alc dep/abuse participants with anxiety disorders had lower auditory P300 amplitudes (7.5 vs. 11.1 μV, $F = 3.5$, 1 *df*, $p = 0.066$), but

Table 4. Relationship of Auditory P300 Amplitude to Alcohol Use and Anxiety Disorders: All Participants

Diagnosis	*n*	P300 amplitude (μV) Mean	SD
Alc+/anx+[a]	9	7.0	6.0
Alc+/anx−[b]	39	9.8	4.4
Alc−/anx+[c]	36	13.4	5.3
Alc−/anx−[d]	114	10.6	4.7

ANOVA: $n = 198$, $F = 6.1$, 3 *df*, $p = 0.0006$.

Pairwise comparisons	*F*	*df*	*p*
Alc+/anx+ vs. Alc−/anx−	4.9	1	0.029
Alc+/anx− vs. Alc−/anx−	1.0	1	0.310
Alc−/anx+ vs. Alc−/anx−	9.0	1	0.003

[a] Alcohol use disorders with anxiety disorders.
[b] Alcohol use disorders without anxiety disorders.
[c] Anxiety disorders without alcohol use disorders.
[d] No alcohol use disorders or anxiety disorders.

nonanxious alc dep/abuse participants did not (10.7 vs. 11.1 μV, $F = 0.2$, 1 *df*, $p = 0.732$). Nonalc dep/abuse participants with anxiety disorders had the highest auditory P300 amplitudes, significantly higher than nonanxious nonalc dep/abuse participants (13.7 vs. 11.1 μV, $F = 4.6$, 1 *df*, $p = 0.033$).

Table 4 shows the results for all 198 individuals ($F = 6.1$, 3 *df*, $p = 0.0006$), and Fig. 1 illustrates the distribution of P300 amplitude across the four groups. In the total group, alc dep/abuse participants with anxiety disorders had significantly lower auditory P300 amplitudes than nonanxious nonalc dep/abuse participants (7.0 vs. 10.6 μV, $F = 4.9$, 1 *df*, $p = 0.029$), and nonalc dep/abuse participants with anxiety disorders had the highest auditory P300 amplitudes (13.4 vs. 10.6 μV, $F = 9.0$. 1 *df*, $p = 0.003$). These results are further illustrated by Fig. 2, which shows group-averaged auditory P300 waveforms at Pz for the four groups. It can be seen that alc dep/abuse participants with anxiety disorders have a strikingly reduced auditory P300 group-averaged amplitude compared with nonalc dep/abuse participants with anxiety disorders. Visual P300 amplitudes were higher in nonalc dep/abuse participants with anxiety disorders compared with alc dep/abuse participants with anxiety disorders [18.1 (SD = 7.0) vs. 13.2 (SD = 4.8) μV, $F = 4.0$, 1 *df*, $p = 0.053$].

Effects of Smoking Status on P300 Amplitude

It was recently shown in the COGA dataset that visual P300 amplitude is significantly reduced in current smokers compared with ex- and nonsmokers, even when corrected for alcoholism (Anokhin et al., 2000). Other studies (Houlihan et al., 1996; Knott et al., 1999) have shown that P300 amplitude, particularly to visual stimuli, is increased by the direct effect of nicotine, whereas some studies show no effect (Lindgren et al., 1999). We had smoking histories on 142 of our participants. Neither auditory ($F = 3.0$, 1 *df*, $p = 0.086$) nor visual P300 amplitude ($F = 0.2$, 1 *df*, $p = 0.644$) was significantly reduced in the 11 nonalc dep/abuse current smokers compared with the 93 nonalc dep/abuse ex- or never-smokers, suggesting that current smoking did not have an effect on P300 amplitude in our study.

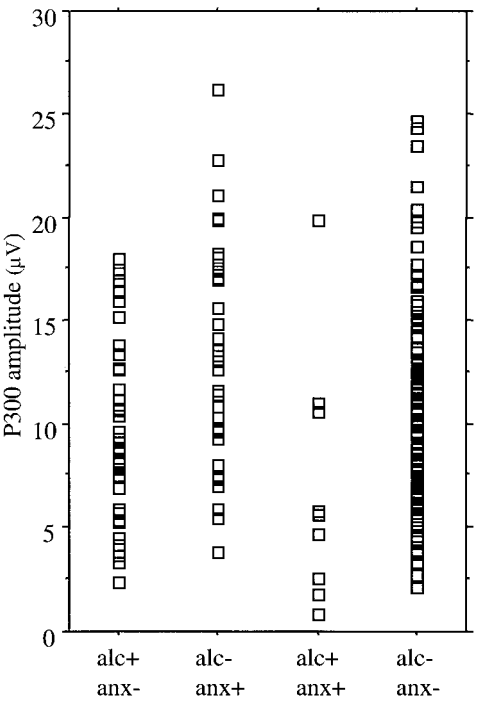

Fig. 1. The distribution of auditory P300 amplitude (μV) in all 198 participants across the four groups: alc+/anx−, alcohol use disorders without anxiety disorders; alc−/anx+, anxiety disorders without alcohol use disorders; alc+/anx+, alcohol use disorders with anxiety disorders; and alc−/anx−, no alcohol use disorders or anxiety disorders.

P300 ERP and Personality Traits

Personality traits were ascertained by means of the EPQ-R. Not all individuals completed all the tests. EPQ-R scores were independent of age. Auditory P300 amplitude showed a modest negative correlation with extroversion in the unrelated participants ($n = 72$, $r = 0.35$, $F = 9.4$, 1 *df*, $p = 0.003$) although the relationship was nonsignificant in the total group ($n = 120$, $r = 0.17$, $F = 3.6$, 1 *df*, $p = 0.060$). Results for visual P300 amplitude were not significant.

DISCUSSION

This study of 198 largely community-derived individuals, including 120 who were unrelated, replicated the finding of lower auditory P300 amplitude in participants with alcohol use disorders compared with those without at Pz, the mid-parietal region, where P300 amplitude is maximal and most heritable. We were particularly interested in a subgroup of alcoholics with anxiety disorders who have been shown to differ in resting EEG α power (Enoch et al., 1999). We found that participants with both alcohol use disorders and anxiety disorders had the lowest auditory P300 amplitudes, whereas alc dep/abuse participants without comorbid anxiety disorders did not differ from nonanxious nonalc dep/abuse individuals (Tables 3 and 4). As predicted, auditory

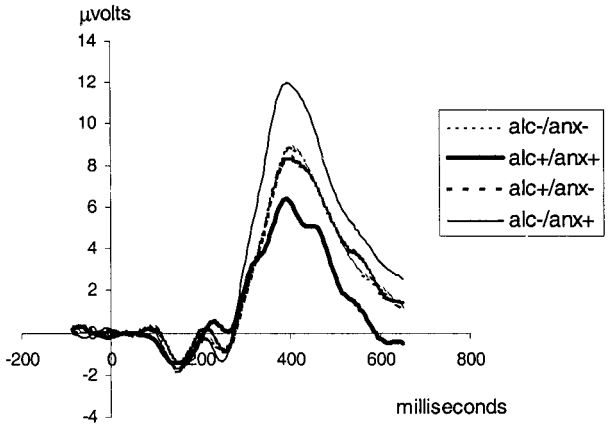

Fig. 2. Group-averaged auditory P300 event-related potentials measured at Pz for all participants (n = 198): alc−/anx−, no alcohol use disorders or anxiety disorders; alc+/anx+, alcohol use disorders with anxiety disorders; alc+/anx−, alcohol use disorders without anxiety disorders; and alc−/anx+, anxiety disorders without alcohol use disorders.

P300 amplitude was negatively correlated with extroversion. This would be expected if lower P300 is a measure of cortical disinhibition (Begleiter and Porjesz, 1999).

Few studies have explored the relationship of P300 response and anxiety traits, particularly when anxiety is comorbid with alcoholism. As hypothesized, auditory P300 amplitudes were significantly increased in the total group of participants with anxiety disorders. This is more likely to represent an underlying trait rather than state effect because participants with anxiety disorders did not have significantly increased scores on the Spielberger State Anxiety Questionnaire, and Spielberger scores were not correlated with P300 amplitude. The greatest range of auditory P300 amplitude was found among individuals with anxiety disorders, with the lowest amplitudes in alc dep/abuse participants with anxiety disorders and the highest amplitudes in participants with anxiety disorders and no comorbid alcohol use disorders (Tables 3 and 4 and Figs. 1 and 2). This suggests that P300 amplitude may distinguish two subgroups of anxiety disorders: low P300 amplitude anxious individuals who are vulnerable to developing alcoholism, some of whom succumb to the disease, and high P300 amplitude anxious individuals with enhanced attention who are not predisposed to alcoholism.

There is a spectrum of disease severity in alcoholism, and previous ERP studies suggest that impaired attentional processing may be more extensive in alcoholics with more severe forms of the disease. Alcoholics with anxiety disorders have been previously shown to have more severe drinking problems, including withdrawal symptoms and increased likelihood of relapse (Johnston et al. 1991; LaBounty et al., 1992; Lotufo-Neto and Gentil, 1994). Nevertheless, in our study we did not find that participants with alcohol use disorders and anxiety disorders had more severe symptoms as measured by age of drinking onset, years of drinking, dependence or abuse, or abstinence or current drinking.

There are several caveats to our findings. The group of participants with alcohol use disorders comorbid with anxiety disorders was small (n = 9), and hence our results concerning this group should be considered preliminary until replicated. There was no sex difference in P300 amplitude, as has been found in some other studies. This may be because the pathology was not severe in our sample of largely community-derived individuals. A small proportion (18%) of the unrelated group came from an outpatient anxiety disorder clinic but contributed 38% of the anxiety disorders. Although P300 amplitudes did not differ between the two groups of anxious subjects, clinic subjects may well experience more severe anxiety symptoms and thus be nonrepresentative of the community.

Results with the visual P300 paradigm were significantly different from some of the results obtained in the auditory paradigm. It may be because the visual task was not sufficiently difficult to reveal group differences; the visual paradigm had been specifically designed so that it could be administered to subjects with a range of ages and intellectual abilities, as typically found in a community sample. However, accuracy of response and reaction times indicated that the subjects had no difficulty with either the auditory or the visual paradigms.

In conclusion, we found that, even in a sample of largely community-derived men and women, auditory P300 amplitude is reduced in individuals with alcohol use disorders, particularly those with anxiety disorders, is increased in nonalc dep/abuse individuals with anxiety disorder traits, and is negatively correlated with extroversion. Our results suggest that there may be two subgroups of individuals with anxiety disorders: those with low auditory P300 amplitudes who are vulnerable to developing alcoholism and those with increased auditory P300 amplitudes who lack the predisposition to alcoholism. However, these results need to be interpreted with caution until they have been replicated in other, larger datasets.

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